IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LEE

Appln. No. 08/966,233

Filed: November 7, 1997

FOR: GDF-1 GENE

Group Art Unit: 1645

Examiner: M. Allen

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July 3, 2000

BRIEF UNDER 37 CFR § 1.191 ET SEQ.

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

A Notice of appeal was timely filed pursuant to Rule 191(a) on February 2, 2000. This brief is now filed in triplicate to appeal the Examiner's final rejection of the pending claims. Reversal of that final rejection is respectfully requested.

A petition and fee for a three-month extension to the due date for this brief is being filed herewith. Thus, it is timely filed because July 1, 2000 was a Saturday.

(1) Real Party in Interest

By assignment recorded on January 16, 1991 starting at reel 5582/frame 0799, rights in the subject invention were assigned to the Carnegie Institution of Washington. An exclusive license was granted to Cambridge NeuroScience who has sublicensed Creative BioMolecules.

(2) Related Appeals and Interferences

The appeal of divisional U.S. Appln. No. 08/971,338 will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) Status of Claims

Claims 3, 11-15, 22 and 24-31 are pending and stand rejected. All other claims have been canceled. The final rejection of all pending claims is appealed.

(4) Status of Amendments

The Examiner made her rejections of claims 3, 11-15, 22 and 24-31 final in the Office Action of November 2, 1999. No amendment of the claims was proposed subsequent to that final rejection. Claims on appeal are set forth in the Appendix.

(5) Summary of Invention

In concise form, the invention of claims 3, 11-15, 22, and 24-31 is directed to the isolation of nucleotide sequences encoding the GDF-1 gene, recombinant molecules comprising those sequences and a vector, cells transformed with such recombinant molecules, and methods of producing recombinant GDF-1 protein.

Support for the claimed invention is shown by original claims 1-3 and 11-15. Particular examples illustrating the claimed invention are the following: Figures 2 and 11A (i.e., nucleotide sequences of mouse GDF-1 transcripts); variant mouse GDF-1 sequences are described on page 19, lines 17-29, and page 28, line 30, to page 29, line 27; Figure 11B (i.e., nucleotide sequence of human GDF-1 transcripts); and Examples 5-6 describe production of GDF-1 protein in prokaryotic and eukaryotic host cells transformed with recombinant molecules.

Original claims 1 and 3 are directed to mammalian GDF-1 genes, especially those derived from mouse, hamster, and human. Figures 5 and 14 show Southern analyses of genomic DNA from mouse, hamster, and human. Example 3 states, "Even at high stringency, the GDF-1 probe detected a single predominant band in both hamster and human DNA (see Figure 5), indicating that GDF-1 is highly conserved across species" (page 22, lines 25-29). Furthermore, Example 8 states, "As shown in Figure 14, both murine and human probes derived from the GDF-1 open reading frame hybridized to the same pattern of bands in human DNA, verifying that the human gene is indeed the homolog of murine GDF-1." (page 31, line 37, to page 32, line 4).

Thus, the invention as presently claimed is fully supported by Appellant's original disclosure.

(6) Issues

A. Under 35 U.S.C. 112, first paragraph, was it proper for the Examiner to reject claim 31 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention (i.e., the "new matter" rejection)?

B. Under 35 U.S.C. 112, first paragraph, was it proper for the Examiner to reject claims 3, 11-15, 22 and 24-30 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to this it pertains, or with which it is most nearly connected, to make and/or use the invention (i.e., the "enablement" rejection)? In particular, does the specification enable an invention directed to a DNA segment encoding mammalian GDF-1 protein having the *amino acid sequence* shown in Figure 2 or 11A or 11B (e.g., claim 22) and a DNA segment encoding mammalian GDF-1 protein comprising a *nucleotide sequence* shown in Figure 2 or 11A or 11B (e.g., claim 23)?

Appellant submits the final rejections are improper for the reasons discussed below and respectfully request their reversal by the Board of Patent Appeals and Interferences (i.e., the "Board").

(7) Grouping of Claims

There are two separate grounds of rejection that apply to the pending claims. Thus, claim 31 does not stand or fall together with claims 3, 11-15, 22 and 24-30. Please note that the following grouping of claims assumes that no new grounds of rejections are entered.

If the Board reverses both the new matter and enablement rejections, then claims 3, 11-15, 22 and 24-31 would be allowable.

But if the Board reverses the new matter rejection and affirms the enablement rejection, then only claim 31 would be allowable.

In contrast, if the Board reverses the enablement rejection and affirms the new matter rejection, then only claims 3, 11-15, 22 and 24-30 would be allowable.

Of course, if the Board affirms both the new matter and enablement rejections, then none of the claims would be allowable.

Furthermore, claim 23 is directed to DNA segments encoding GDF-1 protein having the amino acid sequences shown in Figures 2 or 11A or 11B, while claim 22 is directed to DNA segments comprised of the particular nucleotide sequences shown in the aforementioned figures. Determination by the Board of whether the specification enables the skilled artisan to use the claimed invention (the Examiner has not objected that the specification does not teach how to make the invention) involves two subsidiary issues: (a) does the specification teach how to make and use GDF-1 proteins and (b) does the specification teach how to make and use the particular nucleotide sequences that correspond to GDF-1 genes? Thus, this enablement rejection involves two separate issues which are argued separately below. If the Board finds that Appellant's specification enables a use for the GDF-1 protein, then at least claims 22-23 and claims depending therefrom would be allowable. But if the Board finds that only a use for a nucleotide sequence corresponding to a GDF-1 gene is enabled, then at least claims 23-29 would be allowable.

Therefore, Appellant submits that due to the arguments presented below, the Board should separately consider independent claims 22, 23 and 31 when deciding whether the Examiner's rejections are improper.

(8) Arguments

A. Appellant's Original Disclosure Provides a Written Description for the Invention of Claim 31 Recognizable by the Ordinarily Skilled Artisan

To satisfy the written description requirement, the specification "must clearly allow person of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *In re Gósteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Original claims 1 and 3 demonstrate that Appellant claimed an invention directed to the genus of DNA segments encoding a mammalian GDF-1 protein and particular species of DNA segments derived from mouse, hamster, and human, respectively. The examples of the specification show the isolation of a mouse GDF-1 gene and its use to isolate a human GDF-1 gene. The nucleotide sequences of both are used as non-limiting illustrations of the claimed invention. But the hamster GDF-1 gene is also shown in Figure ~~14~~ 5 by Southern blot analysis using cross-hybridizing mouse or human probes (page 9, lines 1-13) although a hamster cDNA

clone was not isolated and sequenced in this specification. Instead, the existence of the hamster GDF-1 gene was shown by cross-hybridization.

Moreover, Appellant has described his invention in a general manner in the specification starting at page 9, line 15, and continuing to page 10, line 14.

> "The present invention relates to a DNA segment encoding all (or a unique portion) of GDF-1, a member of the transforming growth factor β superfamily. . . .
>
> "The invention further relates to DNA segments substantially identical to the sequence shown in Figure. 2. A "substantially identical" sequence is one the complement of which hybridizes to the sequence of Figure 2 at 68°C and 1M NaCl and which remains bound when subjected at 68°C with 0.1X saline/sodium citrate (SSC) (note: 20 X SSC = 3M sodium chloride/ 0.3 M sodium citrate). The invention also relates to nucleotide fragments complementary to such DNA segments. Unique portions of the DNA segment, or complementary segments, can be used as probes for detecting the presence of respective complementary strands in DNA (or RNA) samples."

Thus, Appellant's intention to claim DNA segments encoding mammalian GDF-1 proteins identified by their ability to cross-hybridize with mouse or human probes is clearly shown by the original disclosure.

Furthermore, the ability to distinguish DNA segments the GDF-1 gene from mammalian genomic DNA is shown in the examples. Example 3 states, "Even at high stringency, the GDF-1 probe detected a single predominant band in both hamster and human DNA (see Figure 5), indicating that GDF-1 is highly conserved across species" (page 22, lines 25-29). Furthermore, Example 8 states, "As shown in Figure 14, both murine and human probes derived from the GDF-1 open reading frame hybridized to the same pattern of bands in human DNA, verifying that the human gene is indeed the homolog of murine GDF-1." (page 31, line 37, to page 32, line 4). Thus, the original disclosure clearly shows that specific hybridization with probes that contain the nucleotide sequences shown in Figure 2 or 11A or 11B uniquely identifies a single DNA segment.

With respect to claim 31 which is drafted in product-by-process format, it should be noted that none of the cases cited by the Examiner have been decided on this basis. Here, in contrast to *Univ. of Calif. v. Eli Lilly and Co.* (43 USPQ2d 1398, Fed. Cir. 1997), the chemical structures of mouse and human GDF-1 have been described and the property of cross-hybridization under particular reaction conditions is explicitly recited in claim 31. Figure 14 shows that stringent hybridization uniquely

identifies the GDF-1 gene. Furthermore, the Federal Circuit has never held that a broad genus of DNA segments could not be claimed by reference to particular nucleotide sequences and their ability to cross-hybridize with the claimed products.

Therefore, because claim 31 is at least explicitly described for the use of a mouse GDF-1 probe and implicitly described for the use of a human GDF-1 probe by the originally filed specification and claims, Appellant respectfully requests that the Examiner's new matter rejection should be reversed by the Board.

B. Appellant's Specification Enables the Skilled Artisan to Make and Use the Invention of Claims 3, 11-15, 22 and 24-30

A rejection based on an alleged lack of enablement requires that evidence, or a reason, be provided by the Examiner to substantiate an assertion that the objective truth contained in the disclosure is doubted. M.P.E.P. § 2164.01. This burden of persuasion has been described by the Office's reviewing court:

> "[I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971).

The Examiner appears to maintain that enablement of Applicant's invention requires working examples showing one or more biological functions of GDF-1. See, for example, pages 4-8 of Paper No. 46. Appellant submits that this is not the proper standard for patentability under Section 112, first paragraph, because the biological function of a protein is only one potential use for his invention. For example, the specification clearly supports the use of GDF-1 as a lineage marker (i.e., "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1," page 12, lines 20-23) and the preparation of probes complementary to GDF-1 transcripts (Example 4) and antibodies directed against GDF-1 (Example 5). The Examiner does not cite a single statute, regulation, or case in support of her proposition that a gene is enabled only by a working example that demonstrates a biological function of the protein encoded by a gene. But without accepting this proposition as a proper statement of the

enablement requirement under Section 112, first paragraph, Appellant has submitted evidence on April 24, 1999 in the form of the Ebendal Declaration that rebuts the Examiner's contention that the biological activity of GDF-1 could not be predicted (see page 3, lines 4-6, of Paper No. 31).

Below, Appellant shows the following: (i) the specification's prediction that GDF-1 can be used as a cell survival molecule in neuronal cultures has proven correct, (ii) the GDF-1 gene as illustrated by the nucleotide sequences shown in Figures 2 and 11A-B can be used as a lineage marker, and (iii) the GDF-1 protein as illustrated by the amino acid sequences shown in Figures 2 and 11A-B can be used as a lineage marker. As discussed above with respect to the Grouping of Claims, if the Board finds that Appellant's specification enables a use for the GDF-1 protein, then at least claims 3, 11-15, 22 and 24-30 would be allowable. But if the Board finds that only a use for the GDF-1 gene is enabled (e.g., Appellant's specification enables the skilled artisan to use GDF-1 gene expression as a lineage marker but that no use of the GDF-1 protein is enabled), then at least claims 23-29 would be allowable.

(i) Use of GDF-1 as a Neuronal Cell Survival Molecule Enables the Invention

Appellant's specification states on page 14, lines 2-8, "If GDF-1 possesses [an activity similar to the nerve cell survival molecule activin], as is indicated by its specific expression in the central nervous system (see below), GDF-1 will likely prove useful *in vitro* for maintaining neuronal cultures for eventual transplantation or *in vivo* for rescuing neurons following axonal injury or in disease states leading to neuronal degeneration." Thus, one biological function of GDF-1 is described by the specification as its potential usefulness as a neuronal cell survival molecule. This function is not a statement of utility added after the filing of the application.

The Examiner reviewed the specification and stated on pages 2-3 of Paper No. 24, "Biological properties are alleged based upon the similarity of the GDF-1 amino acid sequence to the TGF-[β] family. However, there is no evidence of record that this DNA sequence encodes a biologically useful protein possessing any particular properties. (See specification pages 10-11.) The similarities between GDF-1 and the TGF-[β] family members range from 26-52% on the amino acid level and these proteins are not deemed to be predictive of the biological properties possessed by GDF-1. The biological properties of the TGF-[β] family are diverse

and it could not be predicted which activity GDF-1 would have, if any. As such, the specification does not enable using the GDF-1 protein or DNA sequence as disclosed in the specification." Although Appellant did not agree with the Examiner that a biological property of GDF-1 could not be predicted and he maintains that the Examiner has not provided the objective evidence required under *In re Marzocchi* to contest the prediction that GDF-1 acted as a neuronal cell survival molecule, the Ebendal Declaration was submitted to rebut the Examiner's conclusion that GDF-1 activity could not be predicted.

The Ebendal Declaration was submitted on April 24, 1998 and shows that GDF-1 potentiates the effect of neurotrophin-3 (NT-3) protein on neuronal fibre outgrowth in an *in vitro* culture system. Thus, this evidence supports the predicted activity of GDF-1 as a cell survival molecule in *in vitro* culturing of neurons and rebuts the Examiner's allegation that it could not be so predicted. Appellant stresses that the Ebendal Declaration was submitted only to rebut the Examiner's conclusion that GDF-1 activity could not be predicted as done in the specification. The Declaration does not represent an added statement to enable use of GDF-1 protein because, as should be understood by the Board, such post-filing statements would not be effective when it is the specification as originally filed that must teach the skilled artisan how to use the claimed invention. It is the specification's teaching that GDF-1 protein has a potential use as a neuronal cell survival molecule because of its expression in the brain that enables Appellant's claimed invention.

Appellant submits that use of GDF-1 as a neuronal cell survival molecule is both described in the specification and enables his claimed invention.

(ii) DNA Segments Comprising Nucleotide Sequences Shown in Figures 2 and 11A-B Are Enabled by Their Use as a Cell Lineage Marker

Appellant's specification states on page 12, lines 20-23, "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1." The specification also teaches what cell types normally express GDF-1 by illustrating its temporal- and tissue-specific expression in Example 4. Following are descriptions of Northern blots hybridized with a GDF-1 probe:

Figure 6 shows a 1.4 kb transcript was detected in embryos of 8.5 and 9.5 days gestation, but not in later stage embryos. A second RNA species of 3.0 kb appeared at day 9.5 and persisted throughout embryogenesis.

Figure 7 shows that in adult tissues, GDF-1 was expressed almost exclusively in the brain, although GDF-1 was also detected in the adrenal gland, ovary, and oviduct. Thus, restriction of GDF-1 expression to particular adult tissues would be valuable in determining the tissue of origin for a cell.

Thus, as taught in the specification, a GDF-1 probe can be used to determine whether a tumor arose from a cell of the surrounding tissue (i.e., a primary tumor) or was a metastasis from a different tissue. Such a determination often has diagnostic and therapeutic consequences in cancer treatment. Appellant submit this use is both described in the specification and enables his claimed invention.

(iii) DNA Segments Encoding Mammalian GDF-1 Proteins Having the Amino Acid Sequences Shown in Figures 2 and 11A-B Are Enabled by Their Use as a Cell Lineage Marker

As discussed above, Appellant's specification states on page 12, lines 20-23, "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1." This use is not limited to detection of cell-specific expression of GDF-1 transcripts because the GDF-1 protein would also be expressed in a cell-specific manner. Example 5 describes (a) the use of recombinant GDF-1 protein to prepare antibodies directed against GDF-1 and (b) the use of such antibodies in Western blot analysis and immunoprecipitation.

Thus, as an alternative to detection of cell-specific GDF-1 transcription, the GDF-1 protein can be detected directly as a cell lineage marker for the origin of a tumor using an antibody prepared against recombinant GDF-1 immunogen. Appellant submit this use is both described in the specification as "a specific marker for the presence of tumors" and it enables his claimed invention.

* * *

Finally, Appellant submits that the Examiner is being inconsistent in her contention that satisfying Section 112, first paragraph, requires conclusive proof of a gene's biological function. For example, U.S. Patent Nos. 6,008,017 and 6,074,841

contain claims of similar breadth to those on appeal and the specifications fail to provide evidence of the biological function of human cardiac/tolloid-like protein and Don-1 polypeptide, respectively. On the facts of record, there is no explanation why the Examiner has required that Appellant's specification provide working examples that show the biological function of GDF-1 when the specifications of these other patents do not provide such proof.

For the reasons discussed above, reversal of the Examiner's rejection is respectfully requested.

Appellant submits that the pending claims are in condition for allowance and earnestly request an early Notice to that effect. The Board is invited to contact the undersigned if further information is needed.

Respectfully submitted,

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Appendix of Pending Claims

22. An isolated DNA segment encoding mammalian GDF-1 protein having the amino acid sequence defined in an open reading frame of Figure 2 or Figure 11A or Figure 11B.

3. The DNA segment according to claim 22 wherein said mammal is a mouse, or human.

11. A recombinant DNA molecule comprising:

i) said DNA segment according to claim 22, operably linked to

ii) a vector.

12. A host cell stably transformed with said recombinant DNA molecule according to claim 11.

13. The host cell according to claim 12 wherein said cell is a procaryotic cell.

14. The host cell according to claim 12 wherein said cell is a eucaryotic cell.

15. A method of producing a recombinant GDF-1 protein comprising culturing the host cell of claim 12 under conditions such that said GDF-1 protein is produced, and isolating said GDF-1 protein.

24. An isolated DNA segment encoding mammalian GDF-1 protein comprising a nucleotide sequence as defined in an open reading frame of Figure 2 or Figure 11A or Figure 11B.

25. The isolated DNA segment according to claim 24 further comprising a nucleotide sequence outside the open reading frame as defined in Figure 2 or Figure 11A or Figure 11B.

26. A recombinant DNA molecule comprising the isolated DNA segment according to claim 25 operably linked to a vector.

27. A host cell stably transformed with the recombinant DNA molecule according to claim 26.

28. The host cell according to claim 27 wherein said cell is a prokaryotic cell.

29. The host cell according to claim 27 wherein said cell is a eukaryotic cell.

30. A method of producing a recombinant GDF-1 protein comprising culturing the host cell according to claim 27 under conditions such that the GDF-1 protein is produced, and isolating the GDF-1 protein.

31. An isolated DNA sequence complementary to the DNA sequence encoding mammalian GDF-1 protein having the nucleotide sequence defined in Figure 2 or Figure 11A or Figure 11B at hybridization conditions of 68°C and 1M sodium chloride and which remains bound when subjected to washing at 68°C with 15mM sodium chloride/1.5 mM sodium citrate.